jCancer Care Ontario Practice Guidelines Initiative

Sponsored by: Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

Use of Amifostine to Ameliorate the Toxic Effects of Chemotherapy in the Treatment of Cancer

Practice Guideline Report # 12-6

ORIGINAL GUIDELINE: December 1998
MOST RECENT LITERATURE SEARCH: October 2002
NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2003

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Questions

- Does amifostine safely and effectively ameliorate the clinically important side effects of chemotherapy in patients with solid tumours, with acceptable toxicity from amifostine and no significant degree of tumour protection?
- Does amifostine, when added to chemotherapy in patients with solid tumours, result in a meaningful increase in survival and/or an improvement in quality of life, over and above what can be achieved by alternative strategies such as dose reduction of the chemotherapy or drug substitution?

Target Population

These recommendations apply to patients with non-leukemic cancer using conventional doses of alkylating agents and/or moderate or higher doses of cisplatin.

Recommendations

Key Recommendations

- In patients scheduled to receive high per cycle doses of cisplatin ($\geq$100 mg/m^2) or high cumulative doses ($\geq$ 600 mg/m^2), amifostine is a reasonable therapeutic option to reduce the incidence and severity of neurotoxicity, ototoxicity or clinically relevant nephrotoxicity. There are currently no data to determine whether amifostine produces similar benefits at lower per cycle doses or cumulative doses of cisplatin. However, the incidence of neurotoxicity is predicted to rise at cumulative doses of cisplatin $\geq$ 300 mg/m^2 and the use of amifostine could be considered in this setting.
- Amifostine is one of several reasonable therapeutic options to reduce myelosuppression. In assessing the effects of amifostine on quality of life, particularly when amifostine is used as part of palliative treatment, acute toxic effects of amifostine, such as nausea and vomiting and hypotension, need to be weighed against its ability (based on one randomized study) to reduce the morbidity of myelosuppression (episodes of neutropenic fever).

- If the objective of treatment with amifostine is to improve survival by means of dose maintenance of chemotherapy, there is no evidence to justify the routine use of amifostine.

Qualifying Statements

- Although the limited number of randomized controlled trials to date indicate no adverse impact of amifostine on tumour response or survival, the lack of a tumour protective effect in all situations should not yet be automatically assumed. Consequently the use of amifostine in the curative or adjuvant setting should preferably take place in the context of a clinical trial.
- There are limited data regarding the potential for interaction between amifostine and some other cytotoxic agents. Use of amifostine with non-platinum non-alkylating cytotoxic agents should preferably take place in the context of a clinical trial.

Methods

Entries to MEDLINE (through to October 2002), CANCERLIT (through to October, 2002) and Cochrane Library (through to Issue 3, 2002) databases and abstracts published in the 1995-2002 proceedings of the annual meetings of the American Society of Clinical Oncology were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two medical oncologists, one of whom is a member of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Systemic Treatment Disease Site Group (STDSG) and methodologists. This practice guideline has been reviewed and approved by the Systemic Treatment DSG, which comprises medical oncologists, pharmacists and one community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

Thirteen randomized controlled trials (RCTs) that evaluated the effects of amifostine on chemotherapy-induced toxicities were identified: twelve trials compared chemotherapy plus amifostine with chemotherapy alone, and one trial compared chemotherapy plus amifostine with chemotherapy plus granulocyte-colony stimulating factor (G-CSF). Eleven trials used platinum-based regimens in patients with a variety of malignancies, one trial used paclitaxel in patients with metastatic breast cancer, and one trial used mitomycin-C in patients with colorectal adenocarcinoma.

Eight trials showed a trend in favour of amifostine for the protection of bone marrow against the hematologic toxic effects of chemotherapy. One large RCT involving ovarian cancer patients receiving cyclophosphamide and cisplatin showed statistically significant differences in favour of the amifostine group in the number of patients experiencing grade 4 neutropenia in course one (10% vs. 21%; p=0.019), in the number of patients failing to recover from grade 4 neutropenia after courses two to four (44% vs. 65%; p=0.004), and in the number of patients discontinuing treatment due to hematologic toxicity (1% vs. 7%; p=0.016). A smaller RCT involving breast cancer patients treated with paclitaxel with or without amifostine showed no protective benefits for amifostine on any measure of hematologic toxicity. Another RCT involving patients with small-cell lung cancer receiving ifosfamide, carboplatin and etoposide with or without amifostine showed no benefits for amifostine on any measure of hematologic toxicity. A statistically significant difference in favour of amifostine was noted for both the length of hospital stays and the time on antibiotics in one trial reporting these outcomes.

Renal toxicity was measured in six trials, and in all six, amifostine use was associated with significantly favourable outcomes on measures of renal toxicity. Amifostine protection against neurotoxicity (including ototoxicity) was reported in two of the four studies that measured neurotoxicity.

No difference was detected for survival or tumour response rates in the nine studies reporting these outcomes.

The most concerning side effect of amifostine is hypotension during administration, resulting in discontinuation of amifostine in 25% to 62% of those being treated. Nausea and vomiting occurred more often in the amifostine groups in all four trials reporting this outcome. Other, more mild side effects included flushing, sneezing, dizziness, hiccoughs and chills.

Future Research

Data from randomized studies are limited; therefore, it is strongly recommended that patients be enrolled in randomized controlled trials designed to address the effects of amifostine on survival, health care costs, optimal dose, quality of life and pharmacokinetics.

Prepared by the Systemic Treatment Disease Site Group

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PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at:
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